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(54) Title: RADIOPAQUE COMPOSITIONS

(57) Abstract: A radiopaque polymeric composition useful as a polymer coating on a substrate. The compositions are designed to be bioabsorbable and are particularly useful on implantable medical devices, such as vascular prostheses and the like.



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RADIOPAQUE COMPOSITIONS

5 **FIELD OF THE INVENTION**

The present invention relates to polymeric radiopaque materials. More particularly, the present invention relates to biocompatible and biostable radiopaque coatings useful in conjunction with implantable medical devices.

10 **BACKGROUND OF THE INVENTION**

Medical radiography is a well known and important method used for early detection and diagnosis of various disease states of the human body. However, most implantable and non-implantable surgical devices exhibit little absorption of x-ray radiation so that radiographs of both the devices and their environs are difficult to obtain. The ability to see the radiographic image of a medical device being used in or implanted within the body is very important. For example, an implanted medical device, such as an endovascular prosthesis, may need adjustment and monitoring both during and after implantation in the body. Radiographic imaging provides the surgeon with the ability to properly perform such adjustments. Additionally, minimally invasive procedures, which are now very commonplace, require monitoring via radiographic imaging to guide the physician. Devices such as catheters which are not intended to be left for any length of time in the body may employ conventional radiopaque metal markers which are usually disposed at the distal end to indicate the catheter whereabouts in the vessel. Such

radiopaque markers are not useful, however, in implantable devices which are required to be porous and flexible, such as vascular prosthesis. Vascular grafts, including those which are surgically implanted and those which are introduced intraluminally, are designed to mimic the natural vessels and hence require a unique combination of features to be present. The graft must be sufficiently porous to allow cellular ingrowth and encapsulation by the body, yet be fluid-tight to prevent leakage of blood. Additionally, flexibility and compliance are also key features of a successful graft product. Thus, use of metal bands or conventional radiopaque markers are unacceptable in such devices. Moreover, if a radiopaque composition is to be applied as a coating over the graft, it must permit the natural process of cellular ingrowth to occur within the first few weeks of being implanted.

To overcome this problem a variety of conventional approaches have been developed, and numerous patents disclose radiopaque compounds or polymers used in the body.

Radiographic techniques have included the injection of micro-encapsulated particles into the patient which release a radiopaque agent into the body to aid X-ray analysis of tissue and organs which are not otherwise visible by X-rays. For example, U.S. Patent No. 5,342,605 discloses an X-ray contrast composition for oral or retrograde examination of the gastrointestinal tract comprising a divalent cation capable of forming a coating on the tract, and an iodinated radiopaque agent. Gref, et al., U.S. Patent No. 5,565,215 discloses an injectable microparticle for the controlled release of substances for diagnostic imaging that can optionally be targeted to specific organs or cells. While these techniques may be useful for radioscopy of the

gastrointestinal tract and target organs, they do not provide adequate means to detect and monitor medical devices inserted into the body which are otherwise transparent to X-ray imaging.

Moreover, these radiopaque agents are not useful as biostable materials which can be used as polymeric coatings on implantable medical devices such as vascular grafts.

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Furthermore, a number of patents disclose polymeric tubing which includes radiopaque polymer. U.S. Patent No. 3,361,700 discloses a family of alkoxyalkyl esters of diiodobenzoic acid that are radiopaque and suitable to plasticize vinyl resins into a form useful for the manufacture of tubings for catheters and similar products. U.S. Patent No. 3,645,955 discloses that di- and tetraiodoesters are superior for this purpose because they show less tendency to exude from the polymer tubing and can be used in lower concentrations, thereby providing a better balance between flexibility and stiffness of the polymer article. While these compositions are quite suitable for the production of tubing of simple types, they are not completely satisfactory for production of more complicated shaped devices, as they have problems retaining more complex shapes. U.S. Patent Nos. 4,250,072, and 4,283,447 disclose that if the vinyl resin is replaced partially or completely by thermoplastic polyurethane, the iodoester radiopacified compositions are amenable to the induction of complex shapes, i.e., they retain their shape. U.S. Patent No. 4,579,879 discloses employing a controlled amount of platinum-cured silicon network polymers in such tubing to provide a surface which is more hydrophobic and gives a longer service life.

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Neuenschwander, et al., U.S. Patent No. 5,319,059 disclose a biocompatible X-ray

contrasting composition wherein the X-ray contrast material is covalently attached to a polyurethane matrix. However, the polyurethane matrix is unstable, and may be reabsorbed into the body, rendering the article invisible by radiographic imaging. This may be problematic for applications to implantable articles, whose presence would become undetectable to x-rays after decomposition of the x-ray contrast material.

Larsen, European Patent Publication No. 0 203 833, discloses a composition comprising a x-ray contrasting thermoset polymer comprised of a crosslinkable polyester resin which is dissolved in a vinyl monomer. This composition may be used to manufacture surgical articles. However, due to the solid polymer's inflexibility it may not be used to create flexible devices and would certainly be inappropriate to use as any type of prosthetic implant which required flexibility.

Thus, while the prior art has suggested various radiopaque compounds and additives to compositions which are useful in the body, there has yet to be developed a safe, biostable polymeric coating which is easy to apply to the surface of flexible, porous medical devices, such as a vascular graft, and which forms a stable coating. Thus, there is a definite need for a radiopaque polymeric composition which can be particularly useful as a coating for medical devices, and particularly implantable medical devices, and is biocompatible and biostable.

Therefore, it is an object of the present invention to provide such a polymeric radiopaque composition. In particular, the inventive composition is capable of adhering to or becoming part

of a substrate, and capable of forming a flexible film. Furthermore, the inventive composition also possesses an appropriate amount of tackiness, crystallinity and lubricity for use as a medical device coating. Such properties can be obtained in the inventive compositions by tailoring the molecular structure in the polymer groups attached to the radiopaque components.

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The present invention may be applied as a coating to a medical device or may become part of the polymer matrix used to form the device, in either case serving to provide radiopaque character to the device, and thus making the device visible by X-ray imaging techniques.

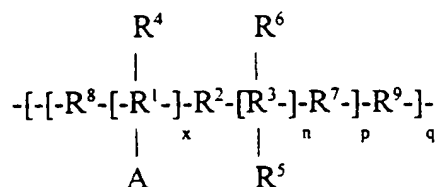
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Furthermore, the present invention utilizes a polymeric composition which displays improved physical properties over prior radiopaque compositions and forms a coating which has a wide adaptable range of physical properties including tackiness, lubricity, hemocompatibility, cell compatibility, and flexibility. The physical characteristics of the polymer are especially important when it is employed on vascular grafts which require natural tissue ingrowth for assimilation into the body. The polymeric radiopaque composition may be tailored to provide a substrate surface which allows the necessary neointimal ingrowth and renders the graft radiopaque, while also maintaining the graft's flexibility.

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SUMMARY OF THE INVENTION

The present invention includes a radiopaque polymeric composition having the formula:



wherein A is a substituted or unsubstituted aromatic or aliphatic group containing a radiopaque component and at least one functional group, said functional group being capable of forming a linkage with R¹ and is selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato, and halo. R¹ and R³ are substituted or unsubstituted aliphatic or aromatic groups having from 1 to 20 carbons, and having at least two reactive ends being the same or different, said reactive ends being selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato, and halo. X is an integer from 1 to 1,000. N is an integer from 0 to 1,000, provided that when n is zero R⁷ is absent. R², R⁷ and R⁸ may be optionally present, and may be the same or different, substituted or unsubstituted groups selected from the difunctional groups consisting of diols, diamines, hydroxy acids and amino acids. R⁴, R⁵, and R⁶ may be the same or different substituents selected from the group consisting of hydrogen, halogen or a hydrocarbon chain having from 1 to 100 carbons. R⁹ is an optional chain extender containing at least two end groups being the same or different and selected from the group consisting of amino, hydroxyl, isocyanate, carbonate, anhydride, acyl chloride, and carboxyl. P is an integer from 1 to 100, and q is an integer from 1 to 100.

DETAILED DESCRIPTION OF THE INVENTION:

The following is a detailed description of the present invention. The description is meant to describe the preferred embodiments, and is not meant to limit the invention in any way.

5 In a preferred embodiment of the present invention the carbon groups of R^1 and R^3 may be polyester, polyether, polycarbonate, polyamide, or a polyester polyamide copolymer.

Polyester is an especially desirous group to attach to the aromatic component because of several advantageous physical properties it imparts.

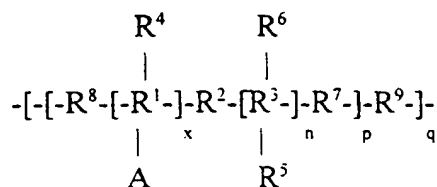
10 The radiopaque polymeric compositions of the present invention need not be cross-linked to perform effectively. The physical properties of the inventive compositions make them very suitable for use as coatings on medical devices. Furthermore, certain portions of the polymeric compositions, i.e., groups R^4 , R^5 , and R^6 may be varied, and depending on the choice of substituents, the composition's properties of adhesion, crystallinity, tackiness, lubricity,
15 hemocompatibility, cell compatibility and flexibility can be controlled.

 In another preferred embodiment of the present invention the radiopaque component of the invention includes an iodinated aromatic ring. In another preferred embodiment of the invention, R^2 of the radiopaque polymeric composition forms an ester group connected to said
20 aromatic or aliphatic group of R^3 . The polyester is optimally attached through the functional groups to a radiopaque component which includes an iodinated aromatic ring.

The compositions of the present invention may be applied as a coating to an implantable or a non-implantable medical device. The compositions of the present invention are suitable to coat substrates of implantable devices because they possess desirous properties of biocompatibility and biostability. Such devices may include, without limitation, catheters, stents, or grafts. A method of imparting the radiopaque polymeric composition to a surface of such a device is also disclosed.

Many of the physical properties of the radiopaque compositions of the present invention can be altered with different compositions some of the components. Specifically, R⁴, R⁵, and R⁶ may be chosen from a variety of different formulations in order to impart characteristics which alter one or more of the composition's properties, said properties being selected from the group consisting of adhesion, crystallinity, tackiness, lubricity, hemocompatibility, cell compatibility, and flexibility.

The present invention also comprises a medical device having at least one radiopaque surface, the radiopaque surface comprising a polymeric composition having the formula:



wherein A is a substituted or unsubstituted aromatic or aliphatic group containing a radiopaque

component and a functional group, said functional group being capable of forming a linkage with R^1 and is selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato, and a halo; R^1 and R^3 are substituted or unsubstituted aliphatic or aromatic groups having from 1 to 20 carbons, and having at least two reactive ends being the same or different, said reactive ends
5 being selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato, and halo; x is an integer from 1 to 1,000 and preferably from 10 to 100; and n is an integer from 0 to 1,000, and preferably from 10 to 100; provided that when n is zero R^7 is absent. R^2 , R^7 , and R^8 may be optionally present, and may be the same or different, substituted or unsubstituted groups selected from the difunctional groups consisting of diols, diamines, hydroxy acids, and amino acids. R^4 ,
10 R^5 , and R^6 may be the same or different substituents selected from the group consisting of hydrogen, halogen, or a hydrocarbon chain having from 1 to 100 carbons. R^9 is an optional chain extender containing at least two end groups being the same or different and selected from the group consisting of amino, hydroxyl, isocyanato, carbonate, anhydride, acyl chloride, and carboxyl. P is an integer from 1 to 100, and q is an integer from 1 to 100.

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The medical device may be a wide variety of devices, and may be implantable or non-implantable. A list of such medical devices includes, but is not limited to catheters, balloons, grafts, surgical felts, stents, nets, PTFE, or any other medical fabrics. Non-medical device uses for the present compositions include engineering, automotive and aerospace applications where
20 diagnostic testing is used.

The present invention also describes a method of imparting a radiopaque polymeric

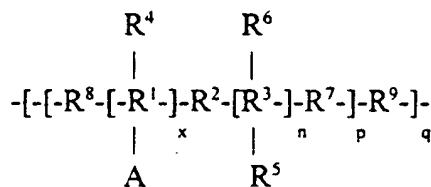
coating of the above formula to a surface of an article by contacting said surface with the radiopaque polymeric composition listed above.

The radiopaque polymeric composition may be applied to a medical device or other article in a variety of ways, including dipping, steeping, or spraying the coating on to the article. A number of layers may be imparted onto the device or article, ranging from 1 to 10 number of layers. In order to apply the polymer to a substrate, the polymeric composition should have a viscosity in a suitable range where it is low enough that it can be sprayed or applied, and high enough to ensure proper application with no problems with adhering the polymeric composition to the substrate.

The radiopaque polymeric coatings of the present invention may be prepared by a variety of chemical reaction routes. The compositions of the present invention may be formed by condensation reactions but is not limited by this type of reaction.

WHAT IS CLAIMED IS:

1. A radiopaque polymeric composition having the formula



wherein A is a substituted or unsubstituted aromatic or aliphatic group containing a radiopaque component and a functional group, said functional group being capable of forming a linkage with R¹ and is selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato, and a halo; R¹ and R³ are substituted or unsubstituted aliphatic or aromatic groups having from 1 to 20 carbons, and having at least two reactive ends being the same or different, said reactive ends being selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato, and halo; x is an integer from 1 to 1,000; n is an integer from 0 to 1,000 provided that when n is zero R⁷ is absent; R², R⁷, and R⁸ may be optionally present, and may be the same or different, substituted or unsubstituted groups selected from the difunctional groups consisting of diols, diamines, hydroxy acids, and amino acids; R⁴, R⁵, and R⁶ may be the same or different substituents selected from the group consisting of hydrogen, halogen, or a hydrocarbon chain having from 1 to 100 carbons; R⁹ is an optional chain extender containing at least two end groups being the same or different and selected from the group consisting of amino, hydroxyl, carbonate, anhydride, acyl chloride, and carboxyl; p is an integer from 1 to 100; q is an integer from 1 to 100.

2. A radiopaque polymeric composition according to claim 1 wherein the substituted or unsubstituted aromatic or aliphatic carbon groups of R^1 and R^3 are a polymeric group, said group being selected from the group consisting of polyester, polyether, polycarbonate, polyamide, or polyester polyamide copolymer.

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3. A radiopaque polymeric composition according to claim 1 wherein R^2 forms an ester group connected to an said aromatic or aliphatic group of R^3 .

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4. A radiopaque polymeric composition according to claim 1 wherein the radiopaque component includes an iodinated aromatic ring.

5. A radiopaque polymeric composition according to claim 1 which is both biocompatible and biodegradable.

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6. A radiopaque polymeric composition according to claim 1 wherein the polymeric composition is not cross linked.

7. A radiopaque polymeric composition according to claim 1 applied to the substrate of a medical device.

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8. A medical device according to claim 6 wherein the medical device is implantable.

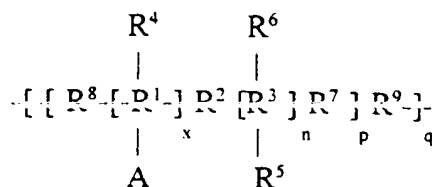
9. A radiopaque polymeric composition according to claim 1 wherein R⁴, R⁵ and R⁶ are chosen to impart characteristics which alter one or more of the composition's properties, said properties being selected from the group consisting of adhesion, crystallinity, tackiness, lubricity, hemocompatibility, cell compatibility, and flexibility.

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10. A medical device having at least one radiopaque surface, said radiopaque surface comprising:

a polymeric composition having the formula

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wherein A is a substituted or unsubstituted aromatic or aliphatic or aliphatic group containing a radiopaque component and a functional group, said functional group being capable of forming a linkage with R¹ and is selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato and halo; R¹ and R³ are substituted or unsubstituted aliphatic or aromatic groups having from 1 to 20 carbons, and having at least two reactive ends being same or different, said reactive ends being selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato, and halo; x is an integer from 1 to 1,000; n is an integer from 0 to 1,000 provided that when n is zero R⁷ is absent; R², R⁷, and R⁸ may be optionally present, and may be the same or different, substituted or unsubstituted groups selected from the difunctional groups consisting of diols, diamines, hydroxy acids, and amino acids; R⁴, R⁵, and R⁶ may be the same or different

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substituents selected from the group consisting of hydrogen, halogen, or a hydrocarbon chain having from 1 to 100 carbons; R⁹ is an optional chain extender containing at least two end groups being the same or different and selected from the group consisting of amino, hydroxyl, carbonate, anhydride, acyl chloride, and carboxyl; p is an integer from 1 to 100; q is an integer
5 from 1 to 100.

11. A medical device according to claim 9 wherein R¹ and R³ of the polymeric composition which comprises the radiopaque surface are a polymeric group, said group being selected from the group consisting of polyester, polyether, polycarbonate, polyamide, or polyester polyamide
10 copolymer.

12. A medical device according to claim 9 wherein the polymeric composition which comprises the radiopaque surface includes an iodinated ring.

13. A medical device according to claim 9 wherein the polymeric composition which comprises the radiopaque surface is both biocompatible and biodegradable.

14. A medical device according to claim 9 wherein the polymeric composition which comprises the radiopaque surface is not cross linked.

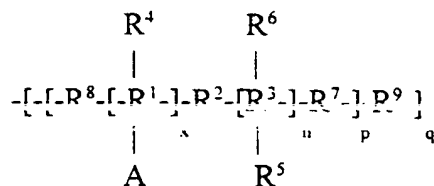
15. A medical device according to claim 9 wherein such device is a graft.

16. A medical device according to claim 9 wherein such device is a stent.

17. A medical device according to claim 9 wherein such device is a catheter.

5 18. A method of imparting a radiopaque polymeric coating to a surface of an article which comprises:

a) contacting said surface with a radiopaque polymeric composition, said composition having the following formula:



wherein A is a substituted or unsubstituted aromatic or aliphatic group containing a radiopaque component and a functional group, said functional group being capable of forming a linkage with R¹ and is selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato, and halo;

20 R¹ and R³ are substituted or unsubstituted aliphatic or aromatic groups having from 1 to 20 carbons, and having at least two reactive ends being the same or different, said reactive ends being selected from the group consisting of carboxyl, amino, hydroxyl, isocyanato, and halo; x is an integer from 1 to 1,000; n is an integer from 0 to 1,000 provided that when n is zero R⁷ is absent; R², R⁷, and R⁸ may be optionally present, and may be the same or different, substituted or
 25 unsubstituted groups selected from the difunctional groups consisting of diols, diamines, hydroxy acids, and amino acids; R⁴, R⁵, and R⁶ may be the same or different substituents selected

from the group consisting of hydrogen, halogen, or a hydrocarbon chain having from 1 to 100 carbons; R⁹ is an optional chain extender containing at least two end groups being the same or different and selected from the group consisting of amino, hydroxyl, carbonate, anhydride, acyl chloride, and carboxyl; p is an integer from 1 to 100; q is an integer from 1 to 100.

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19. The method of claim 17 wherein said article is a medical device.

20. The method of claim 17 wherein said article is a graft.

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21. The method of claim 17 wherein said article is a stent.

22. The method of claim 17 wherein said article is a catheter.

23. The method of claim 17 wherein said contacting is by dipping, brushing or spraying.

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24. The method of claim 17 wherein said contacting further comprises applying from about 0 to 100 layers of the radiopaque polymeric composition to the surface of said article.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/13401

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L29/18 A61L31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61M A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 684 222 A (LONDON HOSPITAL MED COLL) 29 November 1995 (1995-11-29) page 9, line 47 - line 49 claims	1-14, 16, 18, 19, 21, 23
X	WO 98 36013 A (KOHN JOACHIM B ; QIU BO (US); UNIV RUTGERS (US)) 20 August 1998 (1998-08-20) page 14, line 24 - page 15, line 23 claims 1-26	1-16
X	WO 98 59005 A (BAYER AG ; EBERT WOLFGANG (DE); ECKEL THOMAS (DE); WITTMANN DIETER) 30 December 1998 (1998-12-30) claims examples	1-4, 6-12, 14
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

28 September 2000

Date of mailing of the international search report

06/10/2000

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/13401

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 04392 A (HOLMES MICHAEL JOHN ;NYCOMED AS (NO)) 19 March 1992 (1992-03-19) page 18, line 7 - line 17 claims ---	1-15
X	EP 0 452 123 A (BECTON DICKINSON CO) 16 October 1991 (1991-10-16) page 3, line 20 - line 26 page 3, line 57 -page 4, line 3 claims 1,2,6-8 ---	1-4, 6-12,14, 17
X	US 5 780 668 A (SALZ ULRICH ET AL) 14 July 1998 (1998-07-14) claims 1-3 ---	1-4,7-12
X	EP 0 203 833 A (DOW CHEMICAL CO) 3 December 1986 (1986-12-03) cited in the application column 2, line 43 -column 3, line 25 examples 7,8 claims ---	1-4, 7-12,17
X	WO 96 05872 A (BIOMAT BV ;KOOLE LEVINUS H (NL)) 29 February 1996 (1996-02-29) page 6, line 18 - line 36 examples claims ---	1-4, 6-12,14, 16,17
X	US 3 733 397 A (ERIKSON U ET AL) 15 May 1973 (1973-05-15) claims ---	1-4
A	US 4 584 326 A (FLYNN VINCENT J) 22 April 1986 (1986-04-22) claims ---	1-24
A	WO 96 40816 A (PRESS WOLF RUEDIGER ;BAUER MICHAEL (DE); KRAUSE WERNER (DE); MAIER) 19 December 1996 (1996-12-19) claims 1-7 ---	1-24
P,X	WO 99 24391 A (PENDHARKAR SANYOG M ;KOHN JOACHIM B (US); UNIV RUTGERS (US); BOLIK) 20 May 1999 (1999-05-20) page 26, line 19 -page 27, line 21 claims 1-49,65-85 -----	1-24

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,10,18

Present claims 1-24 relate to an extremely large number of possible compounds. In fact, the claims contain so many variables and possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise. As one example of the lack of clarity is the fact that a halo group is not capable of forming a linkage.

However, present claims 1-24 relate to a polymeric composition defined by reference to a desirable characteristic or property, namely radiopaqueness. The claims cover all polymeric compositions defined by a formula in claim 1 having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT nor disclosure within the meaning of Article 5 PCT for any such polymeric compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the polymeric composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to a medical device (stent, catheter, graft) having a radiopaque polymeric composition wherein the radiopaque component includes an iodinated aromatic ring 'cf. claim 4! linked to a polymer backbone selected from the group of polyester, polyether, polycarbonate, polyamide, or polyester polyamide copolymer 'cf. claims 2,4! because of the credibility of the essential features necessary for achieving the result of radiopaqueness.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/13401

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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